THE THREAT OF THINGS BIOLOGICAL

Just as medical science developed the vaccines and drugs believed necessary to conquer infectious diseases such as smallpox, polio, measles, tuberculosis, whooping cough, and diphtheria, a new generation of risks to public health is emerging. Previously unknown infections such as the Ebola virus, HIV/AIDS, Lyme and Legionnaire's diseases, and deadly new strains of *E. coli* and *Staphylococcus* bacteria threaten public health worldwide. In addition, resistance to antibiotics is reaching epidemic proportions according to some scientists, and anthrax spores and botulism toxin have been produced and stockpiled for use as possible biological warfare agents.

In the face of these biological threats, scientists, the public, public health officials, policy makers, and governments are seeking answers to the questions of how to predict the spread of emerging infectious diseases and how to protect against their effects. In assessing the risk of biological agents, decisions will need to be made as to which of these threats to public health are most urgent, how to distribute funds for control and research, and how to provide advice, set public health priorities, and design interventions to deal with the newest versions of the oldest environmental hazards.

What Type of Risk?

The processes employed by scientists to assess and quantify risks differ depending on whether the threat is a chemical or physical hazard or a biological agent. Epidemiology, the study of the distribution and dynamics of diseases through human populations, provides a scientific basis for the evaluation of risk from biological agents. Most epidemics of infectious disease are characterized by acute symptoms that appear after relatively short incubation periods and can be reliably diagnosed from clinical signs and laboratory tests. Infectious disease epidemiologists can determine "attack rates," or the relative infectiousness and survival rates for infectious diseases. From these and other data, including the availability and effectiveness of treatments, they can also ascertain the severity of risk from uncontrolled disease outbreaks as compared to other infectious diseases. Epidemiologists also use mortality rates or incidence of severe disabilities to calculate "years of potential life lost" or "years of potential productivity lost" from

debilitating infectious diseases such as maternal rubella infection or polio. Such estimates are used to support recommendations for funding of prevention programs for infectious diseases and other public health problems.

Although epidemiology is also a valuable discipline in helping to characterize risks from long-term, chronic exposures to environmental chemical and physical hazards, there are fundamental differences between these exposures and effects and those associated with biological agents. Environmental chemical exposures are most often associated with chronic diseases with long incubation periods, and multiple etiologies. Their effects are not easily diagnosed in the early stages by either physical examination or laboratory studies. The risks to human health from hazardous chemical exposures often must be weighed against the benefits of economic and industrial development and an abundant food supply. Balancing risks with benefits implies the ability to accurately measure risks. If these risks are unacceptably high, regulations implementing engineering and other controls are enacted to manage them. Unlike most chemical hazards, disease-causing biological agents are generally viewed as naturally occurring entities with no associated benefit.

Throughout the 1960s and 1970s, public concern about environmental chemicals and radiation increased and worries about infectious disease declined. Federal agencies were created and given broad regulatory responsibilities for environmental, occupational, and consumer product safety. These agencies adopted a process called risk assessment to identify and quantify the health risks from exposures to chemical and physical agents. In March 1983, the National Academy of Sciences' National Research Council (NRC) published *Risk Assessment in the Federal Government: Managing the Process.* The study was commissioned by Congress to assist federal regulatory agencies in strengthening the reliability and objectivity of scientific assessments that provide a basis for regulatory policies applicable to chemical carcinogens and other nonbiological public health hazards. The report defined quantitative risk assessment as a four-step process:

- Hazard identification—the determination of whether a particular chemical is or is not causally liked to particular health effects;
- Dose–response assessment—the determination of the relationship between the magnitude of exposure and the probability of occurrence of the health effect in question;
- Exposure assessment—the determination of the extent of human exposure before or after the application of regulatory controls;
- Risk characterization—the description of the nature and often the magnitude of human risk, including attendant uncertainty.

The NRC report validated the fundamental principles of quantitative risk assessment used by federal regulatory agencies for environmental and occupational hazards, and risk assessment has become the fundamental tool used by environmental public health experts to estimate the magnitude of the threat to public health from chemical and physical hazards.

Biological Risk Assessment

Assessing the risk to human health from biological agents has taken a separate course. While federal research funding for cancers and other chronic diseases with presumed environmental etiologies increased, infectious and communicable disease programs and research have not fared as well. According to some critics, policy makers have assumed that modern vaccines, good sanitation, and food safety would continue to reduce the incidence of communicable diseases. To a limited extent, this optimism has been warranted, but it has failed to anticipate either the ability of biological agents to evade the armaments of modern medicine or the emergence of new, virulent infections that defy the best of modern medicine.

In 1973, smallpox virus escaped from a laboratory in London, causing widespread public alarm and initiating international efforts to assure that infectious agents in laboratories and research institutions are regulated and controlled. In the United States, the Centers for Disease Control and Prevention (CDC) developed guidelines for laboratory safety that include four levels of containment of human pathogens based on the magnitude of the risk of the agent to human health if released:

- Level 1—no or very low individual and community risk. The microorganism is unlikely to cause human or animal disease;
- Level 2—moderate individual risk and low community risk. The pathogen can cause human or animal disease but is unlikely to be a serious hazard to laboratory workers, the community, livestock, or the environment. Laboratory-acquired exposures may cause serious infection, but effective treatment and preventive measures are available and the risk of spread of infection is limited;
- Level 3—high individual risk and low community risk. The pathogen usually causes serious human or animal disease but does not ordinarily spread from one infected individual to another. Effective treatment and preventive measures are available;
- Level 4—high individual risk and community risk. The pathogen usually causes serious human or animal disease and can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventive measures are not usually available.

Under prevailing World Health Organization (WHO) convention, each member nation assigns biological agents to one of these categories based on such variables as pathogenicity, modes of transmission, levels of immunity in the local population, presence and control of vectors, and availability of preventive and therapeutic measures. In the United States, the CDC makes these determinations. The scientific process for classifying well-characterized pathogens such as smallpox is rather straightforward. But for emerging infectious diseases where data are limited, decisions must be based on preliminary epidemiological data, modeling, and a public health tradition that dictates the most conservative approach to unknown risks.

HIV/AIDS is one of the emerging infectious diseases for which policy makers and the public demanded estimates of risk to public health when very little data were available. According to Philip Cooley, a statistician and survey research expert at Research Triangle Institute in Research Triangle Park, North Carolina, once the retrovirus that causes AIDS had been identified and characterized, "Our priority was to model the spread of the infection so that public health officials could reliably publicize the risks of disease from various sexual and/or drug use behaviors." He adds, "These models were also critical to epidemiologists in making estimates of the spread of the HIV/AIDS epidemic in high-risk populations." The earliest HIV/AIDS risk models were based heavily on assumptions, and like the earliest assessments of chemical risks, they suffered from limited data characterizing the hazard or delineating the routes of exposure and dose response. However, as scientists tested the assumptions and as research provided more data, the models have became more accurate predictors. According to Cooley, the major value of modeling the spread of an emerging infectious disease through the population is in developing control strategies for emerging infectious diseases. For example, in the 26 July 1996 issue of *Science*, Sally Blower, a researcher in the

department of biostatistics and epidemiology at the University of California at San Francisco, presents a theoretical framework for an eradication strategy for tuberculosis (TB) in developed and emerging nations. Blower modeled the transmission of TB in patients and derived estimates of the minimum treatment levels of patients and their contacts needed to eradicate TB. Cooley notes that "Blower has assimilated much of the seminal work in modeling the spread of infectious disease epidemics into a practical set of recommendations to the control of the worldwide tuberculosis epidemic." However, critics charge that while such models provide health officials with the elements to potentially reduce disease rates and control epidemics, they do not offer comparative quantifications of the magnitude of risks from biological agents.

Pathogens are selected as potential biological warfare and terrorism agents based on their high probability of causing a very high incidence of death or severe incapacitation. If such agents were used, scientists predict that the victims would overwhelm the health care delivery system and traditional public health interventions for protecting the general population. This reality is addressed in the August 1997 issue of the *Journal of the American Medical Association*, which is devoted entirely to the threat of biological warfare and biological terrorism. David Franz, a veterinary pathologist at the U.S. Army Medical Research Institute of Infectious Diseases at Ft. Detrick, Maryland, and lead author of the survey article on clinical recognition and management, included estimates prepared by the WHO in 1970 that, for example, 50 kg of *Bacillus anthracis* dispensed from an aircraft 20 km upwind of a city of 500,000 would kill 220,000 people. Franz's paper provides information on recognition, diagnosis, and treatment of the diseases caused by the pathogens most likely to be used by terrorists. Franz argues for a system of surveillance by physicians educated to recognize and report diseases caused by bioterrorism agents. The system would alert health officials quickly so that appropriate therapy could be initiated and the impact of a terrorist attack greatly reduced. He advocates education of all private physicians in the diagnosis and treatment of diseases caused by biological warfare and bioterrorism agents. But these measures have not yet taken place, in part because such programs would be expensive and present significant logistical difficulties. Measures such as creating a national surveillance system, manufacturing, stockpiling, and properly storing vaccines, and putting a vaccine delivery system in place to immediately immunize thousands of citizens face similar challenges.

Taking Measures

The federal Anti-Terrorism Act authorized the CDC to issue risk-based regulations controlling the transfer and use of hazardous agents in the United States with the goal of preventing access for use in domestic or international terrorism. The CDC issued regulations in April 1997 that identified 24 infectious agents and 12 toxins that pose a significant risk to public health. These biological agents were selected based on the threat posed to human health from exposure, the contagiousness of the agent, the ease of methods by which the agent is transmitted through the population, and the availability and effectiveness of immunization and treatment. Both Franz and CDC experts point out that surveillance by physicians educated to recognize and report diseases caused by these restricted biological agents would alert health officials quickly so that appropriate therapy could be initiated and the impact of a terrorist attack greatly reduced.

Arnold Kaufmann, a medical epidemiologist recently retired from the CDC, and Martin Meltzer, a CDC health economist, writing in the April–June 1997 issue of the *Journal of Emerging Infectious Diseases*, modeled the impact of a terrorist attack using *B. anthracis* and estimated risks as measured by the economic costs. They reported a cost of $26.2 billion per 100,000 persons exposed. They argue that the nation cannot afford to not develop a system of surveillance, and establish a program to assure rapid, post-attack prophylaxis. Using an economic argument for interventions to protect human health from the risks of biological agents is a step toward harmonization of the differences between risk assessments for chemical and biological hazards. Another example of the convergence of the approaches to these problems and the scientific methods to assess risk can be found in recent proposals to improve food safety.

The World Trade Organization adopted the International Agreement on the Application of Sanitary and Phytosanitary Measures to give guidance to countries in developing consistent regulations to control the food-borne human and plant pathogens that may be imported on foods. Under the international covenant, these regulations must be risk-based. Anna Lammerding, chief of microbial food safety risk assessment for Health and Welfare Canada, proposes using the four-step process used in quantitative risk assessment for environmental chemicals as a "new strategy for evaluating and managing food safety risks that arise from changes in pathogens, food preparation, distribution, consumption, and population immunity that have the potential to adversely affect human health." Nell Ahl, director of the U.S. Department of Agriculture's (USDA) Office of Risk Assessment and Cost Benefit Analysis, compares and contrasts toxicological and chemical risk assessments developed over the past 30 years with the procedures used to assess risks from imported plant pests and livestock diseases, as well as food safety for human health. Ahl says, "Biological risk assessments present great challenges because of the variability of individual pathogens as well as [the fact that] the variability of individuals affected by these pathogens adds another level of complexity." She adds, "The USDA uses scenario or pathway analysis and probabilistic methods to trace the hazard from the initiating event to the occurrence of the hazard, making use of probability density functions to express what is known and what is not known about the movement of the hazard through the pathway." The USDA has not yet formally adopted these procedures, nor have they become the standard for justifying the regulations controlling the import of human and plant pathogens on foods and other agricultural products into the United States. Ahl wants to be sure that the four-step process delineated in the NRC report can be adapted in a scientifically rigorous manner for biological purposes. Lammerding is quite optimistic that the quantitative risk-assessment model for chemical hazards can be adapted. She and her colleagues are using it as the general approach to assessing risks from food-borne pathogens.

The 1983 NRC report concluded, "Dissatisfaction with the actions of federal regulatory agencies is often expressed as criticism of the conduct and administration of the risk assessment process. The committee believes that the basic problem in risk assessment is the sparseness and uncertainty of the scientific knowledge of the health hazard addressed, and this problem has no ready solution. The field has been developing rapidly and the greatest improvements in risk assessment result from acquisition of more and better data, which decreases the need to rely on inference and informed judgment." Clearly this statement is true today for both chemical and biological risk assessments. In particular, as recognition grows that both old and new infectious agents continue to threaten public health, assessing these risks is dependent on aggressive pursuit of scientific knowledge and a rational process to use this knowledge to quantitate these risks and to design effective interventions.

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